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MANUAL FOR OBSTETRICS & GYNECOLOGY PRACTITIONERS

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Federation of Obstetric & Gynaecological Societies of India



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4 Amenorrhea

Saswati Sanyal Choudhury

INTRODUCTION

Menstruation is the hallmark of reproductive ability in human beings. Amenorrhea is defined as complete absence of menstruation. Incidence varies from 3–4% of reproductive age group.[1]

Primary amenorrhea is said to be present when the women never had menstruation by the age of 16 years in presence of normal growth and secondary sexual characters or 14 years in absence of normal growth and development of secondary sexual characters.

Secondary amenorrhea is defined absence of menstruation for a length of time equivalent to total of at least three of the previous cycle interval or 6 months in a woman who was menstruating before. Secondary amenorrhea is more common than primary amenorrhea.[2,3] Although there is a long list of the causes of secondary amenorrhea, the most common causes are PCOS, hyperprolactinemia, premature ovarian failure and hypothalamic amenorrhea.

For having normal menstruation a lady must have the following functions and structures intact:

- Normal continuously patent outflow tract consisting of uterus cervix and vagina
- Well-coordinated function of hypothalamo-pituitary-ovarian axis
- Normal functional endometrium in the uterus.

For diagnostic evaluation (Flow chart 1) segregating causes of amenorrhea causes can be put in 4 compartments but one has to add up other endocrine disorders like thyroid, adrenal and exogenous hormone-induced amenorrhea like post-pill amenorrhea.

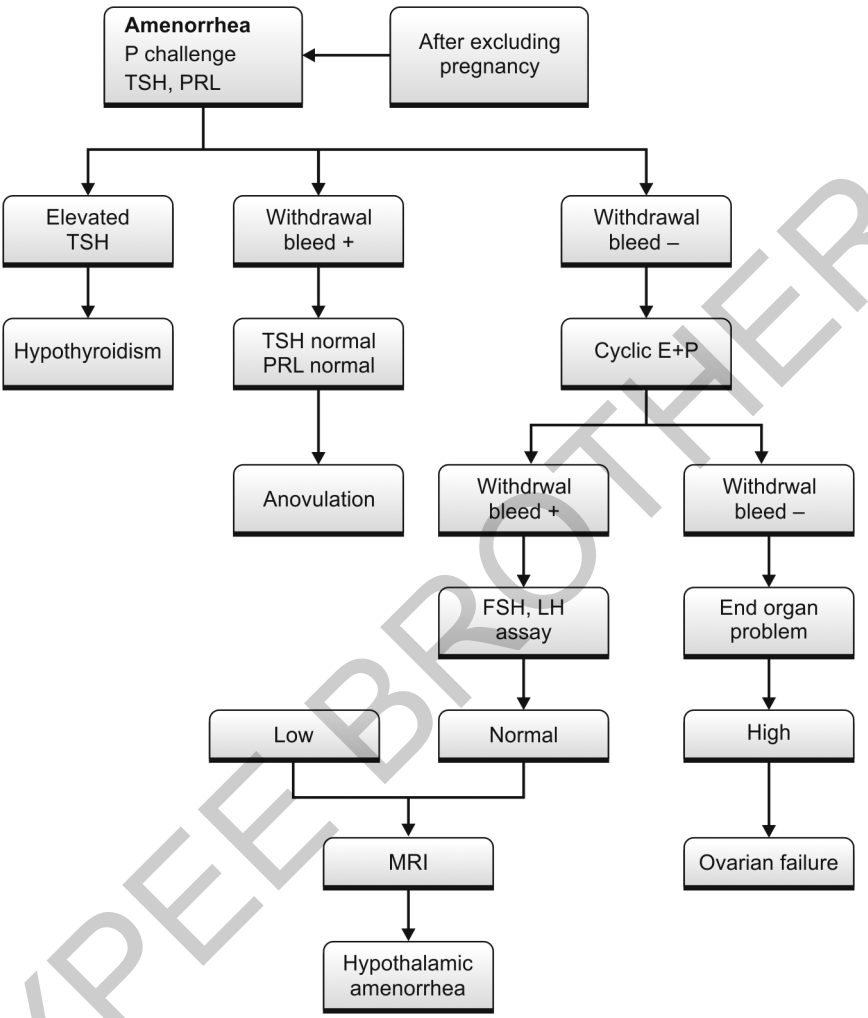
1. Disorders of outflow tract or uterine target organ.
2. Disorders of ovary.
3. Disorders of pituitary.
4. Disorders of CNS.

EVALUATION OF AMENORRHEA (FLOW CHART 2)

Although etiology of primary or secondary amenorrhea is extensive, the evaluation is straightforward. Most important part like any other disease is detailed history and clinical examination. Exclusion of pregnancy is a must as all reproductive age group women with amenorrhea should be assumed pregnant unless proved otherwise. Evidence for psychological dysfunction and emotional stress should be looked for. Family history of genetic defects, food habit, CNS disease, galactorrhea and presence of normal reproductive tract are the other

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Flow chart 1 Diagnosis of secondary amenorrhea



Abbreviations: P, progesterone; TSH, thyroid–stimulating hormone; PRL, prolactin; FSH, follicle–stimulating hormone; LH, Luteinizing hormone

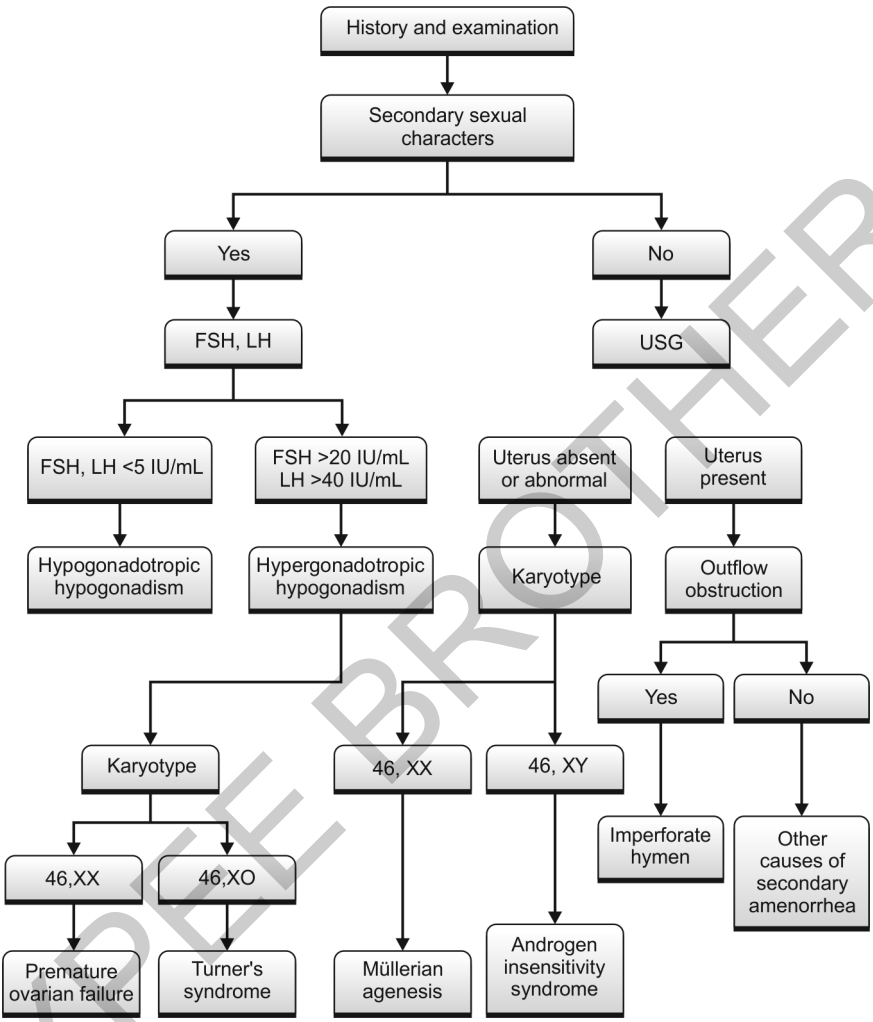
essential areas of importance in history and examination. After complete history and thorough physical examination which includes stigmata of chromosomal defects investigation should be offered step-by-step.[2]

Step I

Initial step would be progesterone challenge test, estimation of thyroid and prolactin level. Idea of PCT is to establish endogenous presence of estrogen and presence of normal outflow tract if there is bleeding after medication.

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Flow chart 2 Algorithm for evaluation of primary ammenorrhea



Step II

If there is no withdrawal bleed next step consists of giving combined estrogen and progesterone and if there is no bleeding in presence of normal outflow tract then end organ insensitivity is established which may be due to Asherman syndrome or tubercular endometritis.

Step III

If there is bleeding with estrogen and progesterone, the next step will be gonadotropin measurement as positive test means absence of estrogen

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production by ovaries due to hypogonadism. To differentiate hypogonadotropic from hypergonadotropic hypogonadism, FSH/LH estimation is necessary.

If the patient shows high prolactin level without hypothyroidism she will need CT/MRI of sella turcica for pituitary imaging to exclude micro or macroadenoma or prolactinomas.

To establish abnormality in outflow tract MRI can give the best result.

To diagnose premature ovarian failure (POF) serum AMH, inhibin B is a better option than FSH/LH level and once diagnosis of POF is confirmed, screening for autoantibody, galactosemia, fragile X syndrome may be offered to find out the etiology of the condition.[4]

Causes of Primary Amenorrhea

The relative prevalence of primary amenorrhea includes hypergonadotropic hypogonadism (48.5% of cases), hypogonadotropic hypogonadism (27.8%), and eugonadism (pubertal delay with normal gonadotropins; 23.7%).

The hypergonadotropic hypogonadism category includes patients with abnormal sex chromosomes (Turner syndrome), who make up 29.7% of all primary amenorrhea cases and those with normal sex chromosomes. The latter group includes both patients who are 46,XX (15.4%) and those who are 46,XY (3.4%) (Table 1).

Hypogonadotropic hypogonadism includes the following:

- Congenital abnormalities
- Endocrine disorders
- Tumor
- Systemic illness (2.6%)
- Eating disorder (2.3%).

Table 2 illustrates the causes of secondary menorrhea.

Congenital abnormalities that can cause hypogonadotropic hypogonadism include the following:

- Isolated GnRH deficiency
- Forms of hypopituitarism
- Congenital central nervous system (CNS) defects
- Constitutional delay.

Table 1 Clinical differential diagnosis of primary amenorrhea

Presence of uterus	*Breast development*	*No breast development*
Present	Similar to secondary amenorrhea	Hypothalamic amenorrhea Pituitary amenorrhea Gonadal dysgenesis 17α-hydroxylase deficiency (46,XX)
Absent	Müllerian agenesis Androgen insensitivity syndrome	Testicular regression 17,20-desmolase deficiency 17α-hydroxylase deficiency (46,XY)

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Table 2 Causes of secondary amenorrhea[3,5,6]

- Secondary amenorrhea with normal ovarian function (Eugonadotropic-normal FSH, LH)
  - Asherman's syndrome
  - Endometrial destruction (tuberculosis, schistosomiasis, irradiation)
- Secondary amenorrhea with decreased ovarian function
  - High gonadotropins
    - Premature ovarian failure—autoimmune, mumps, galactosemia, genetic, chemotherapy, 17-hydroxylase deficiency syndrome, idiopathic
    - Surgical castration
    - Radiation castration
    - Gonadal dysgenesis—Turner's mosaics
  - Low or normal gonadotropins
    - Functional aberrations of the hypothalamic-pituitary axis
      - Psychogenic
      - Nutritional-starvation, anorexia nervosa, bulimia
      - Exercise-induced
      - Pseudocyesis
      - Central nervous system lesions
      - Nongonadal endocrine disorders (thyroid, adrenal, pancreas)
      - Pharmacologic (postpill, psychotropic drugs, drug addiction)
      - Systemic infectious and chronic diseases—chronic liver disease, CRF, diabetes, immunodeficiency, inflammatory bowel disease
      - Idiopathic
      - Kallmann syndrome
      - Sheehan's syndrome
    - Neoplastic, vascular, or traumatic central nervous system disease
    - Feminizing ovarian tumors
- Secondary amenorrhea with increased androgen secretion
  - Polycystic ovary syndrome
  - Masculinizing ovarian tumors
  - Acromegaly
  - Cushing's disease
  - Exogenous androgens
  - Nonclassical CAH
- Hyperproactinemia
  - Prolactin <100 ng/mL
    - Breastfeeding, breast stimulation
    - Hypothyroidism
    - Pharmacologic—H_2 receptor antagonist, antidepressant, antipsychotics, opiates, cocaine, antihypertensive
    - Altered metabolism—liver failure, renal failure
    - Ectopic production—bronchogenic carcinoma, gonadoblastoma, renal cell carcinoma, teratoma
  - Prolactin >100 ng/mL—pituitary microadenoma, macroadenoma, empty sella syndrome

Endocrine disorders that can cause hypogonadotropic hypogonadism include the following:

- Congenital adrenal hyperplasia (CAH)
- Cushing's syndrome
- Pseudohypoparathyroidism
- Hyperprolactinemia.

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Tumors that can cause hypogonadotropic hypogonadism include the following:

- Unclassified pituitary adenoma
- Craniopharyngioma
- Unclassified malignant tumor

Eugonadism may result from anatomic abnormalities or intersex disorders. Anatomic abnormalities include congenital absence of the uterus and vagina (CAUV) and cervical atresia. Intersex disorders include androgen insensitivity, 17-ketoreductase deficiency, and inappropriate feedback.

MANAGEMENT

Treatment of amenorrhea depends on the cause and need for fertility. Operative intervention for some Müllerian obstruction gives excellent result like vaginal septum, imperforate hymen. Hysteroscopic adhesiolysis for Asherman's syndrome is the choice of treatment and conception rate varies from 33–58% depending on the severity.

Removal of tumors of pituitary and brain tumors in selected cases and treating prolactinomas with dopamine agonists like bromocriptine and cabergoline give very encouraging results.

Psychological counseling for feeding disorders and normalization of body weights in anorexia Nervosa and bulimia cases is the treatment of choice.

Correction of thyroid disorders restores normal menstruation. For chronic anovulation, COC or progesterone is used if patient does not need conception. For premature ovarian failure cases, COC is given. Hypogonadotropic hypogonadism is treated with gonadotropins like FSH and LH or pulsatile GnRh analogue.

Successful management of amenorrhea depends upon correct diagnosis and assessment of the needs. Each woman will have different priority starting from fertility issues, hirsutism, delayed secondary sexual development, risk of osteoporosis and endometrial protection from unopposed estrogenic action and treatment must focus on these issues for the best possible care of this very common problem of reproductive period.

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MANUAL FOR
OBSTETRICS & GYNECOLOGY
PRACTITIONERS

Written by National experts in the field of Obstetrics and Gynecology the book serves as a ready reckoner for practitioners on the clinical situations that are most likely to be encountered. A manual which gives precise and evidence-based algorithms, standard investigations and treatment protocols for quick decision making in common situations and would also act as a guide to what should be done when things do not go well.



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